

REMARKS

Previously, claims 136-159, 162-170, 173-190, 193-197 and 202-204 were pending. In the instant amendment, claims 156-159, 162-170, 173-190, 193-197, and 202 have been canceled without prejudice to Applicants rights to pursue canceled subject matter in one or more related applications. Claims 136, 138, 139, and 154 have been amended. Claims 205-226 have been added. Upon entry of the amendment, claims 136-155, and 203-226 will be pending and under consideration.

In addition to the present patent application, Applicants' other patent applications Serial Nos. 10/164,690 and 10/231,895 (Attorney Docket Nos. 11134-006-999 and 11134-007-999, respectively) that relate to CXCR3 modulators are pending before the Patent Office.

I. AMENDMENT TO THE CLAIMS

Claims 156-159, 162-170, 173-190, 193-197, and 202 have been canceled without prejudice.

Support for the amendments to claims 136, 138, and 139 is found, for example, on page 19, lines 7-8 of the specification and claims 51, 56, and 57 as originally filed, and found in Provisional Application 60/296,499, for example, at page 17, lines 27-28.

Support for the amendment to claim 154 is found, for example, on page 25, line 29, to page 26, line 24, and claims as originally filed.

New claim 205 corresponds to claim 136 prior to the instant amendment.

New claims 206, 207 and 217 are supported, for example, by claims 3, 68, and 99 as originally filed.

New claims 208 and 218 are supported, for example, by the specification at page 19, line 7, and at page 20, line 6, as originally filed.

New claims 209 and 219 are supported, for example, by claims 75 and 106 as originally filed.

New claims 210 and 220 are supported, for example, by the specification at page 19, lines 25-27 as originally filed.

New claims 211, 212, 221 and 222 are supported, for example, by claims 57, 84 and 115 as originally filed.

New claims 213 and 223 are supported, for example, by claims 58, 83, 84, 114 and 115 as originally filed.

New claims 214 and 224 are supported, for example, by claims 59 and 116 as originally filed.

New claims 215 and 225 are supported, for example, by claims 88 and 103 as originally filed.

New claims 216 and 226 are supported, for example, by claims 89 and 120 as originally filed.

As the amendments to the claims are fully supported by the specification and claims as originally filed, entry thereof is respectfully requested. No new matter has been added. No amendment fee is believed to be due, since the total number of claims with the instant amendment is less than number of claims previously paid for by Applicants.

II. PRIORITY UNDER 35 U.S.C. § 119(e)

The Patent Office alleges that Provisional Application 60/296,499 (the “‘499 application”) fails to provide adequate support under 35 U.S.C. § 112 for a claim of priority under 35 U.S.C. § 119(e) with respect to the pending claims. The Patent Office acknowledges that the ‘499 application supports variables A⁴, X, R¹, R², Q, L, subscript n, R_a, R³, R⁴, R⁹, R¹⁰ and R¹¹ as recited in the instant claims. However, the Patent Office alleges that instant variable R¹⁴ is broader than that disclosed in the ‘499 application.

Claim 136 as amended in variable R¹⁴ is fully supported in the ‘499 application under 35 U.S.C. § 112, first paragraph, for example, at page 17, lines 27-28. For this reason, the ‘499 application fully supports claim 136, claims 137-152 that depend from claim 136, and claims 153-155, 203 and 204 that encompass the use of the compound of claim 136. Accordingly, Applicants respectfully request the withdrawal of the objection to Applicants’ claim of priority under 35 U.S.C. § 119(e) to Provisional Application 60/296,499.

III. OBJECTION TO CLAIMS 156, 157, 170, AND 190 UNDER 37 C.F.R. § 1.75(c)

The Patent Office objects to claims 156, 157, 170, and 190 under 37 C.F.R. § 1.75(c) as being in an improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully disagree and do not acquiesce in this objection. Nonetheless, in order to expedite prosecution, Applicants have canceled claims 156, 157, 170, and 190, and submit that the objection to these claims is moot in view of their cancellation. Applicants respectfully request the withdrawal of the objection to claims 156, 157, 170, and 190 under 35 U.S.C. § 112, second paragraph.

IV. RESPONSE TO CLAIM REJECTIONS

A. Rejection of Claims 187, 190 and 202 Under 35 U.S.C. § 112, Second Paragraph

Claims 187, 190 and 202 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly because the phrase “a CXCR3-mediated condition or disease” recited in claim 187 is indefinite. Applicants respectfully disagree and do not acquiesce in this rejection. Nonetheless, in order to expedite prosecution, Applicants have canceled claims 187, 190 and 202, and submit that the rejection to these claims is moot in view of their cancellation. Applicants respectfully request the withdrawal of the rejection of claims 187, 190 and 202 under 35 U.S.C. § 112, second paragraph.

B. Rejection of Claims 154-159, 162-170, 173-190, 193-197, and 202 Under 35 U.S.C. § 112, First Paragraph

Claims 154-159, 162-170, 173-190, 193-197, and 202 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly for requiring undue experimentation to practice across their scope, *i.e.*, non-enablement. Although Applicants respectfully disagree and do not acquiesce in the rejection of claims canceled in the instant amendment, nonetheless the rejection to these claims is moot in view of their cancellation.¹ Applicants respectfully traverse the rejection of pending claims 154 and 155, for reasons explained below.

It appears that the Patent Office’s rejection under 35 U.S.C. § 112, first paragraph, stems from the perceived breadth of both the diseases to be treated and the compounds to be used. Although the perception that these two variables render the claim non-enabled is legally improper, Applicants have amended claim 154 to recite methods of treating a subset of diseases of interest.

Claim 154 as amended recites a “method of treating psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, organ transplant conditions, or multiple sclerosis in a subject . . . comprising administering to a subject . . . a therapeutically effective amount of the compound of Claim 136.” Claim 155 depends from claim 154.

The Patent Office’s concern that an “apparently limitless and unknown list of diseases” are embraced within claim 154 is moot. For these reasons alone, the rejection should be withdrawn. However, the Patent Office’s other concerns are addressed below.

The Patent Office contends that claim 154 embraces a huge number of compounds that would have to be synthesized, screened and tested in order to determine if any particular

¹ Claims 156-159, 162-170, 173-190, 193-197, and 202 that stand rejected under 35 U.S.C. § 112, first paragraph, for non-enablement, have each been canceled in the instant amendment.

example is, in fact, useful for treating a disease. The Patent Office instructs Applicants to look at the U.S. District Court decision of *University of Rochester v. G.D. Searle*, No. 00-CV-6161L, 2003 U.S. Dist. LEXIS 3030 (W.D.N.Y. Mar. 5, 2003), a case in which the court indicated that the application in question did not identify any suitable compound. In the instant application, however, the compounds are set forth in the specification and in claim 136. Indeed, numerous specific examples of the compounds as well as methods of making the compounds are set forth in the specification, and representative biological activity of these examples are provided in Figure 19.

The Patent Office is concerned that the chemical formula of the compound to be used for treating the recited diseases is overly broad. Given the teaching of the specification, this concern is misplaced. As stated by the Federal Circuit, a disclosure such as in the instant application is sufficient to meet the enablement requirement:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Brana, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (quoting *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971)). The Patent Office presents no valid reason to object to statements made to as the utility of the compounds in the instant application.

In sum, claim 154 encompasses the use of a compound having the formula as recited in claim 136. The specification teaches how to make and use the full scope of the genus of compounds claimed. For instance, the specification provides numerous species and exemplary methods of synthesizing these compounds (*see, e.g.*, page 34 to page 162). The specification clearly discloses utilities for these compounds as CXCR3 modulators and for treating disease. Moreover, the specification presents an assay in which one of skill in the art can determine CXCR3 modulatory activity without undue experimentation (see Example 12 of the specification at page 162). Therefore, Applicants respectfully submit that the method claims are enabled over the full scope of the recited genus.

To the extent that the Patent Office has confused a utility rejection with an enablement rejection, Applicants address the erroneous utility rejection next. For example, the Patent Office states that “Applicants have not asserted and it is not art-recognized that the results of this *in vitro* assay are correlated to clinical efficacy of any disease treatment.”² Moreover, the Patent Office cites *Ex parte Jovanovics*, 211 U.S.P.Q. 907 (Bd. App. 1980), *In re Langer*, 183 U.S.P.Q. 288 (CCPA 1974), *Hoffman v. Klaus*, 9 U.S.P.Q.2d 1657 (Bd. App. & Int. 1988), which may be in error since none of these decisions even have an enablement question in issue; each of these decisions is specifically concerned with utility under 35 U.S.C. § 101.³ Even so, the legal requirements of utility for claims 154 and 155 are met.

The legal standard of utility requires that the Patent Office must provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility at which point the burden shifts to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention’s asserted utility. *See In re Brana*, 34 U.S.P.Q.2d 1436, 1441-42 (Fed. Cir. 1995) (explaining further that clinical trials or FDA approval are not prerequisites for finding usefulness). Clearly, those of ordinary skill in the art recognize the utility of compounds that act to modulate T-cell trafficking or CXCR3 signaling (*see, e.g.*, Qin *et al.*, 1998, *J. Clin. Invest.* 101:746-754, Balashov *et al.*, 1999, *Proc. Natl. Acad. Sci. USA* 96:6873-6878).⁴ As explained in the specification, the selective expression of CXCR3 makes it an ideal target for intervention to interrupt inappropriate T-cell trafficking (page 3, lines 1-2), thus positive results of CXCR3 modulation in an assay such as described in the specification (*see* pages 162-163 and Figure 19) are sufficiently convincing to those of skill in the art of the usefulness of a compound as claimed for the treatment of the recited diseases. Hence, the instant method claims have the requisite utility under 35 U.S.C. § 101, and furthermore, are fully enabled by the specification pursuant to 35 U.S.C. § 112, first paragraph.

For the reasons explained above, Applicants respectfully request that the rejection of claims 154-159, 162-170, 173-190, 193-197, and 202 stand under 35 U.S.C. § 112, first paragraph, be withdrawn.

² Office Action dated October 9, 2003, page 12.

³ Applicants were unable to locate the additional decision of “*Ex parte Powers*, 200 USPQ 925” as cited by the Patent Office.

⁴ Copies of these references were included in the Amendment and Response mailed September 15, 2003.

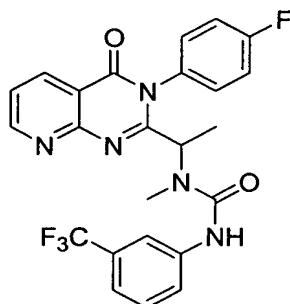
C. Claim Rejections Under 35 U.S.C. § 103

1. Obviousness Rejection in view of U.S. Patent No. 6,545,005 (“Baxter '005”)

Claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168-170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202 stand rejected under 35 U.S.C. § 103(a), allegedly for being obvious over U.S. Patent No. 6,545,005 (“Baxter '005”). Although Applicants respectfully disagree and do not acquiesce in the rejection of claims canceled in the instant amendment, nonetheless the rejection to these claims is moot in view of their cancellation.⁵ Applicants traverse the rejection of the claims 136-139, 142, 143, 145, 147, 149 and 153-155.

The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound. *In re Lalu*, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984); *In re Jones*, 21 U.S.P.Q.2d 1941, 1944 (Fed. Cir. 1992). In this case, the Patent Office acknowledges that compound (20) of Baxter '005 is not encompassed within the formula of claim 136. Moreover, the Patent Office does not explain where the motivation is found in order to make the proposed molecular modifications to make compound (20) within the formula recited in instant claim 136. Applicants respectfully submit that the Patent Office has not made a case of *prima facie* obviousness since the Patent Office has not supplied a motivation or suggestion, in Baxter '005 or otherwise, to alter the compound (20) to result in compounds encompassed within the scope of claim 136 or the claims that depend from claim 136.

The Patent Office alleges that Baxter '005 teaches the two modifications to compound (20) that are necessary for compound (20) to be within the genus recited in claim 136. Compound (20) in Baxter '005 has the structure:



One structural modification requires that the urea linkage in compound (20) be replaced with an amide linkage, for which the Patent Office cites Baxter '005, at column 32, lines 30-31,

⁵ Claims 156-158, 162, 163, 165, 166, 168-170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202 that stand rejected under 35 U.S.C. § 103 have each been canceled in the instant amendment.

which states “[i]n certain related embodiments, X-Y-Z taken together represents urea (NC(O)N) or an amide (NC(O) or C(O)N).” Taken in its proper context, this definition of X-Y-Z applies to the generic formula II (shown in column 31 of Baxter ’005) amidst numerous definitions of the variables R₁, R₂, L, X, Y, Z, R₈, W, subscript p, and subscript n. There is no suggestion or motivation why one of skill in the art would select this particular definition of X-Y-Z to be applied to compound (20), as opposed to the other numerous definitions of the variables R₁, R₂, L, X, Y, Z, R₈, W, subscript p, and subscript n provided by Baxter ’005. Even so, this molecular rearrangement of compound (20) is not sufficient for it to be encompassed within the genus recited in claim 136.

The second structural modification of compound (20) discussed by the Patent Office is that the methyl group attached to the nitrogen must be substituted in order to fit within the definition of “-L-R³” radical in the instant claim 136. However, there is no suggestion or motivation in Baxter ’005 for making this specific alteration. The Patent Office cites Baxter ’005, column 30, lines 50-56, which states “R₈, independently for each occurrence, represents H, lower alkyl, -(CH₂)_naryl (e.g., substituted or unsubstituted), -(CH₂)_nheteroaryl (e.g., substituted or unsubstituted), or two R₈ taken together may form a 4- to 8-membered ring, e.g., with X and Z, which ring may include one or more carbonyls,” as providing the alleged suggestion, specifically in the included recitation of “alkylene-heteroaryl.” Nothing in Baxter ’005 points to modifying the methyl group attached to the nitrogen compound (20) with an alkylene-heteroaryl group specifically, since the cited definitions of R₈ when taken in their proper context, apply to the generic formula II (shown in column 30 of Baxter ’005) amidst numerous definitions of the variables R₁, R₂, L, X, Y, Z, R₈, W, subscript p, and subscript n. There is no suggestion or motivation why one of skill in the art would select any of the alternative definitions, much less the alkylene-heteroaryl, of R₈ to be applied to compound (20).

Applicants respectfully submit that the Patent Office is not relying knowledge which was within the level of ordinary skill to arrive at the claimed invention, but rather the Patent Office is picking and choosing sections of Baxter ’005 using the instant application as a guide to arrive with the claimed invention, which is legally improper.

In connection with making the necessary molecular modifications to compound (20), the Patent Office contends that the “medicinal chemist seeking to improve the potency and efficacy of his compounds can easily explore [the combinations taught by Baxter ’005].” As explained above, Baxter does not explicitly teach the necessary molecular modifications to compound (20). Also, that a medicinal chemist could easily explore different substituents to

put into compound (20) is not a legally proper standard, but rather that the prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound. *In re Lalu*, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984); *In re Jones*, 21 U.S.P.Q.2d 1941, 1944 (Fed. Cir. 1992). In addition, the usefulness of the compounds disclosed by Baxter '005 are in their potency and efficacy as hedgehog antagonists, not as CXCR3 modulators and/or anti-inflammation agents as are the compounds in the instant application. To Applicants' knowledge, there is no reason to suspect that hedgehog antagonists have molecular structures that would be similar to CXCR3 modulators. The Patent Office has not explained how Baxter '005 is relevant in directing those of skill in the art towards the compound of claim 136.

Baxter '005 merely discloses generic formula encompassing a very large number of compounds and nowhere does Baxter '005 indicate that with respect to any particular embodiment, such as compound (20), that certain variables should be specifically targeted for molecular rearrangement in order to be encompassed by the compound of claim 136, or in claims 137-139, 142, 143, 145, 147, 149, and 153-155 that depend from claim 136. Therefore, Applicants respectfully submit that the Patent Office has not made a case of *prima facie* obviousness. Accordingly, Applicants respectfully request that the rejection of claims 136-139, 142, 143, 145, 147, 149 and 153-155 under 35 U.S.C. § 103(a) be withdrawn.

2. Obviousness Rejection in view of WO 01/19800

Claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168-170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202-204 stand rejected under 35 U.S.C. § 103(a), allegedly for being obvious over Baxter (WO 01/19800) essentially for the reasons cited with regard to Baxter '005 discussed above. Although Applicants do not acquiesce in the rejection, the rejection is moot with regard to claims 154-158, 162, 163, 165, 166, 168-170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202 since these claims have been canceled. Applicants traverse the rejection of claims 136-139, 142, 143, 145, 147, 149 and 153.

The Patent Office contends that claims 31-39 of Baxter (WO 01/19800) are drawn to compound (20) when in fact this is clearly not possible since the only independent claim of claims 31-39, *i.e.*, claim 31, defines a generic formula wherein variable X is -NH-. Compound (20) does not fall within the generic formula of claim 31 since the equivalent to variable X in compound (20) is -N(CH₃)-. Thus, nothing in claims 31-39 of Baxter (WO 01/19800) can be understood to apply to substitutions to the chemical structure of

compound (20). Furthermore, the definitions of variables for generic formulas in other parts of Baxter (WO 01/19800) do not suggest or motivate those of ordinary skill in the art to alter the molecular structure of compound (20) for reasons similar to those explained above in regard to Baxter '005. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 136-139, 142, 143, 145, 147, 149, and 153 under 35 U.S.C. § 103(a).

V. ALLOWABLE SUBJECT MATTER

Applicants acknowledge the Patent Office's recognition that, although claims 140, 141, 144, 146, 148, 150-152, and 203 are objected to as being dependent upon a rejected base claim, these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In this case, Applicant have not rewritten these claims into independent form, pending resolution of the status of the base claim in view of the foregoing remarks.

Also, the Patent Office included claim 202 in the list of claims that would be allowable if rewritten, although it would appear that claim 204 was perhaps the claim that the Patent Office meant to include rather than claim 202. Confirmation of which method claim was intended to be included would be much appreciated.

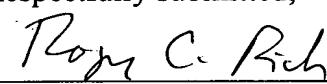
CONCLUSION

In view of the above remarks, the subject application is believed to be in good and proper order for allowance.

No fees are believed due with this response. However, the Commissioner is authorized to charge any fees under 37 C.F.R. § 1.17, any underpayment of fees, or credit any overpayment to Pennie & Edmonds U.S. Deposit Account No. 16-1150 (order no. 11134-005-999) that may be required by this Amendment and Response.

Respectfully submitted,

Date: January 8, 2004

54,398
Roger C. Rich (Reg. No.)
For: Anthony M. Insogna (Reg. No. 35,203)

JONES DAY
12750 High Bluff Drive
Suite 300
San Diego, CA 92130
(858) 314-1200